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(21) International Application Number: PCT/US00/13410 (22) International Filing Date: 16 May 2000 (16.05.00) (30) Priority Data: 09/313,048 17 May 1999 (17.05.99) US (71) Applicant (for all designated States except US): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 1111 Franklin Street, 12th floor, Oakland, CA 94607-5200 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CARSON, Dennis, A. [US/US]; 14824 Vista Del Oceano, Del Mar, CA 92014 (US). COTTAM, Howard, B. [US/US]; 1890 Lendee Drive, Escondido, CA 92025 (US). DENG, Lynn [CN/US]; 16435 Armstead Street, Grenada Hills, CA 91344 (US). (74) Agent: MCCrackin, Ann, M.; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.																																																																		
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<table border="1"> <caption>Estimated data from the graph</caption> <thead> <tr> <th>Concentration (μM)</th> <th>8b (% of control)</th> <th>8a (% of control)</th> <th>ROLIPRAM (% of control)</th> <th>SB-210313 (% of control)</th> </tr> </thead> <tbody> <tr> <td>0.03</td> <td>95</td> <td>95</td> <td>85</td> <td>95</td> </tr> <tr> <td>0.06</td> <td>90</td> <td>110</td> <td>90</td> <td>90</td> </tr> <tr> <td>0.1</td> <td>80</td> <td>90</td> <td>85</td> <td>85</td> </tr> <tr> <td>0.2</td> <td>65</td> <td>75</td> <td>80</td> <td>75</td> </tr> <tr> <td>0.5</td> <td>30</td> <td>55</td> <td>70</td> <td>60</td> </tr> <tr> <td>1</td> <td>15</td> <td>25</td> <td>65</td> <td>50</td> </tr> <tr> <td>2</td> <td>10</td> <td>15</td> <td>55</td> <td>45</td> </tr> <tr> <td>5</td> <td>5</td> <td>10</td> <td>50</td> <td>40</td> </tr> <tr> <td>10</td> <td>5</td> <td>10</td> <td>50</td> <td>35</td> </tr> <tr> <td>20</td> <td>5</td> <td>10</td> <td>50</td> <td>30</td> </tr> <tr> <td>50</td> <td>5</td> <td>10</td> <td>50</td> <td>25</td> </tr> <tr> <td>100</td> <td>5</td> <td>10</td> <td>50</td> <td>20</td> </tr> </tbody> </table>				Concentration (μM)	8b (% of control)	8a (% of control)	ROLIPRAM (% of control)	SB-210313 (% of control)	0.03	95	95	85	95	0.06	90	110	90	90	0.1	80	90	85	85	0.2	65	75	80	75	0.5	30	55	70	60	1	15	25	65	50	2	10	15	55	45	5	5	10	50	40	10	5	10	50	35	20	5	10	50	30	50	5	10	50	25	100	5	10	50	20
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THIAZOLOPYRIMIDINES USEFUL AS TNF α INHIBITORS

Background of the Invention

(This invention was made with the support of NIH Grant No. BM23200.

5 The Government has certain rights in the invention.)

The release of inflammatory cytokines such as IL-1 and tumor necrosis factor-alpha (TNF α) by leukocytes is a means by which the immune system combats pathogenic invasions, including infections. TNF α stimulates the expression and activity of adherence factors on leukocytes and endothelial cells, 10 primes neutrophils for an enhanced inflammatory response to secondary stimuli and enhances adherent neutrophil oxidative activity. See, Sharma et al., Med. of Inflamm., 6, 175 (1987). In addition, macrophages/dendritic cells act as accessory cells processing antigen for presentation to lymphocytes. The lymphocytes, in turn, become stimulated to act as pro-inflammatory cytotoxic 15 cells.

Generally, cytokines stimulate neutrophils to enhance oxidative (e.g., superoxide and secondary products) and nonoxidative (e.g., myeloperoxidase and other enzymes) inflammatory activity. Inappropriate and over-release of cytokines can produce counterproductive exaggerated pathogenic effects through 20 the release of tissue-damaging oxidative and nonoxidative products (K. G. Tracey et al., J. Exp. Med., 167, 1211 (1988); and D. N. Männel et al., Rev. Infect. Dis., 2 (suppl. 5), S602-S606 (1987)). For example, TNF α can induce neutrophils to adhere to the blood vessel wall and then to migrate through the tissue to the site of injury and release their oxidative and non-oxidative 25 inflammatory products.

Although monocytes collect slowly at inflammatory foci, given favorable conditions, the monocytes develop into long-term resident accessory cells and macrophages. Upon stimulation with an inflammation trigger, monocytes/ macrophages also produce and secrete an array of cytokines (including TNF α), 30 complement, lipids, reactive oxygen species, proteases and growth factors that remodel tissue and regulate surrounding tissue functions.

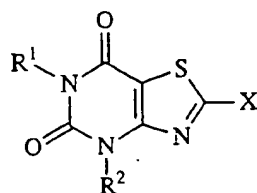
- Inflammatory cytokines have been shown to be pathogenic in: arthritis (C.A. Dinarello, Semin. Immunol., **4**, 133 (1992)); ischemia (A. Seekamp et al., Agents-Actions-Supp., **41**, 137 (1993)); septic shock (D. N. Männel et al., Rev. Infect. Dis., **9** (suppl. 5), S602-S606 (1987)); asthma (N. M. Cembrzynska et al., Am. Rev. Respir. Dis., **147**, 291 (1993)); organ transplant rejection (D. K. Imagawa et al., Transplantation, **51**, 57 (1991)); multiple sclerosis (H. P. Hartung, Ann. Neurol., **33**, 591 (1993)); and AIDS (T. Matsuyama et al., AIDS, **5**, 1405 (1991)). In addition, superoxide formation in leukocytes has been implicated in promoting replication of the human immunodeficiency virus (HIV) (S. Legrand-Poels et al., AIDS Res. Hum. Retroviruses, **6**, 1389 (1990)).

- A series of substituted xanthine-like compounds including pteridinediones, quinazolinones, and isoquinolones have been reported which inhibit the production or action of $\text{TNF}\alpha$ in human monocytes stimulated with lipopolysaccharide (LPS) *in vitro*. See, for example, H. B. Cottam et al., J. Med. Chem., **35**, 2 (1996) and D. Carson et al. (U.S. Patent No. 5,843,943). The most active compounds of these series were found to be in the pteridinedione class and their activity was independent of phosphodiesterase inhibition. Moreover, these compounds bind only very weakly at adenosine receptors A_1 and A_{2a} and therefore elevations in intracellular cyclic AMP levels are unlikely to play a significant role in their biological activity.

However, a continuing need exists for compounds which can block the deleterious effects of the cytokine-mediated mammalian inflammatory response.

Summary of the Invention

- The present invention provides thiazolopyrimidines of formula (I):



(I)

wherein R^1 is -Z-A wherein Z is (a) C_1 - C_7 alkyl, optionally comprising 1-2 double bonds, 1-2 nonperoxide O or 1-2 NR wherein R is individually H,

phenyl, C₂-C₄ alkanoyl, benzyl or C₁-C₆ alkyl; (b) C₃-C₆ cycloalkyl; (c) C₃-C₆ cycloalkyl C₁-C₃ alkyl; (d) C₆-C₁₀ aryl; or (e) C₆-C₁₀ aryl C₁-C₃ alkyl;

A is N(R)₂, C₂-C₄ acyloxy, SO₃H, PO₃H₂, N(NO)(OH), SO₂NH₂, PO(OH)NH₂, OH, SO₂R³ tetrazolyl, or COOR³, wherein R³ is H, phenyl, benzyl
5 or C₁-C₆ alkyl optionally substituted with 1-2 OR, C₆-C₁₀ heteroaryl, C₆-C₁₀ aryl, C₂-C₄ alkenyl, phenyl, tetrazolyl or an ester of an amino acid;

R² is a C₁-C₆ alkyl, C₂-C₄ alkenyl, C₆-C₁₀ aryl C₁-C₂ alkyl or C₆-C₁₀ heteroaryl C₁-C₂ alkyl;

X is H, halo, OR, SR, N₃ or N(R)₂; or a pharmaceutically acceptable salt
10 thereof.

Preferably, R¹ is -(CH₂)_nA wherein n is 2-6, wherein 1-2 CH₂ can optionally be replaced by 1-2 nonperoxide O or NH; or R¹ is phenyl substituted with A, i.e., 4-A-phenyl; A is preferably CO₂R³; X preferably is N(R)₂ wherein each R is individually H, (C₁-C₄)alkyl, C₂-C₄ alkanoyl, or phenyl; preferably, H
15 or CH₃.

These compounds are derivatives of the thiazolo[4,5-d]pyrimidine ring system and are also xanthine-like. When compared to the compounds of U.S. Patent No. 5,843,943, the compounds of formula I can exhibit a 10- to 20-fold increase in potency as anti-TNF α agents. Thus, *in vitro* studies indicate IC₅₀
20 values of less than 500 nM for certain compounds of formula I. *In vivo* experiments in mice show certain of these compounds to have oral activity in a model of acute inflammation, while not exhibiting significant toxicity.

Compounds of formula (I) are inhibitors of TNF α release and can be useful to treat those diseases where overproduction of proinflammatory
25 cytokines has been shown to play a major role. These may include autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, asthma, psoriasis and inflammatory bowel disease. Other conditions, such as cardiomyopathy and congestive heart failure, and insulin-resistant diabetes, can also be treated using the present compounds.

30 Certain of the compounds of formula (I) are useful as intermediates in the preparation of other compounds of formula (I), e.g., as depicted below.

Brief Description of the Figures

Figure 1 is a graph depicting the effect of compounds of the invention on TNF α production in human monocytes using ELISA.

Figure 2 is a graph depicting the effect of **8b** and **8a** on IL-1B production
5 in human monocytes using ELISA.

Figure 3 is a graph depicting the effect of **8a** and **8b** on Jurkat cell growth using the MTT assay.

Figure 4 is a graph depicting the activity of compounds of the invention as Type IV PDE inhibitors vs. rolipram in the U937 cell extract.

Figure 5 is a graph depicting the **8a** dose response on LPS-induced TNF α
10 stimulation.

Figure 6 is a graph depicting the **8a** time course on LPS-induced acute inflammation.

Figure 7 depicts the arthritis scores of untreated mice and mice treated
15 with **8a** over time.

Detailed Description of the Invention

The following definitions are used, unless otherwise described. Halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, aralkyl, alkylaryl, etc. denote both
20 straight and branched alkyl groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl includes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached
25 via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of nonperoxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C₁-C₄)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a
30 benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

The term "amino acid ester" encompasses the product of the reaction of a hydroxy group with the carboxy group of an N-protected amino acid, optionally following by removal of the protecting group. Useful amino acids include the "protein amino acids" and the di- and tri-peptides thereof listed on page 391 of Remington's Pharmaceutical Sciences (18th ed.). These esters can be prepared by the procedures of H. Han et al., Pharmaceutical Res., **15**, 1154 (1998).

Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, or enzymatic techniques, by synthesis from optically active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine adenosine agonist activity using the tests described herein, or using other similar tests which are well known in the art.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

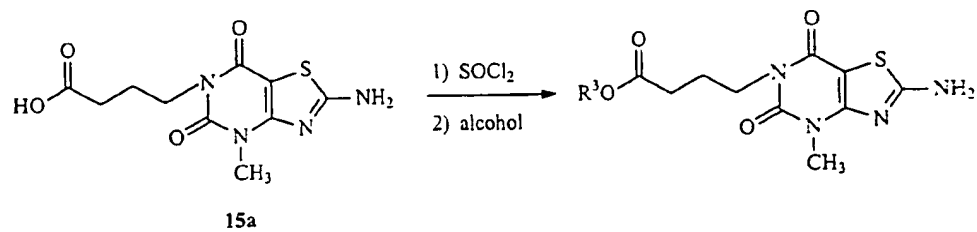
Specifically, C₁-C₇ alkyl can be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, 3-pentyl, hexyl or heptyl; (C₃-C₆)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; (C₃-C₆)cycloalkyl(C₁-C₆)alkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl; 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, or 2-cyclohexylethyl.

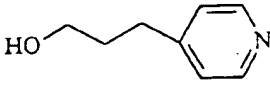

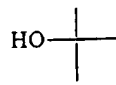
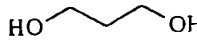
As used herein, the term "cycloalkyl" encompasses bicycloalkyl, (norbornyl, 2.2.2-bicyclooctyl, etc.) and tricycloalkyl (adamantyl, etc.), optionally comprising 1-2 NH, O or S.

(C₁-C₄) alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec- or butoxy, (C₂-C₄)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, (C₂-C₆)alkanoyl can be acetyl, propanoyl, butanoyl or pentanoyl; halo(C₁-C₇)alkyl can be iodomethyl,

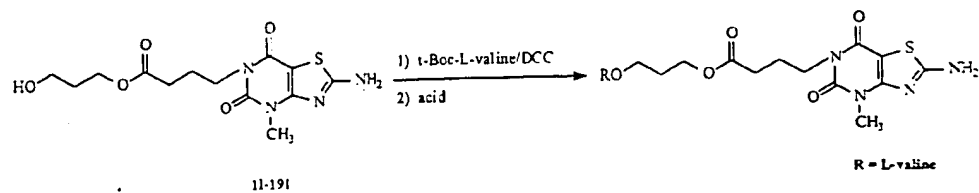
- bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl, hydroxy(C₁-C₆)alkyl can be hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 4-hydroxybutyl, 1-hydroxypentyl, 5-hydroxypentyl, 1-hydroxyhexyl, or 6-hydroxyhexyl; (C₁-C₄)alkoxycarbonyl (CO₂R³) can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, or butoxycarbonyl; (C₁-C₄)alkylthio can be methylthio, ethylthio, propylthio, isopropylthio, butylthio, or isobutylthio; (C₂-C₆)alkanoyloxy can be acetoxy, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, or hexanoyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).
- 15 A specific value for X is amino, monomethylamino or dimethylamino.
A specific value for R¹ is carboxy(C₁-C₇)alkyl, (C₁-C₄)alkoxycarbonyl(C₁-C₇)alkyl, 3-N-pyridylpropyloxycarbonyl(C₁-C₇)alkyl; or 3-hydroxypropyloxycarbonyl(C₁-C₇)alkyl, and the 3- α -amino acid esters thereof.
- 20 Preferably, C₁-C₇ alkyl in R¹ is -CH₂CH₂CH₂-.
A specific value for the ester of the amino acid is the L-valine or L-glycine ester.
A specific value for R² is H, methyl, ethyl, propyl or phenyl.
- Compounds of formula (I) can be synthesized by the procedures of J. A. Baker et al., J. Chem. Soc. (c), 2478 (1970), and modified by the general procedures set forth in U.S. Patent Nos. 5,843,943 and 5,877,180.
- 25 Preferred compounds of formula (I) and then syntheses are depicted below on Table 1 and in Schemes 1-4.

Table 1. Ester Derivatives

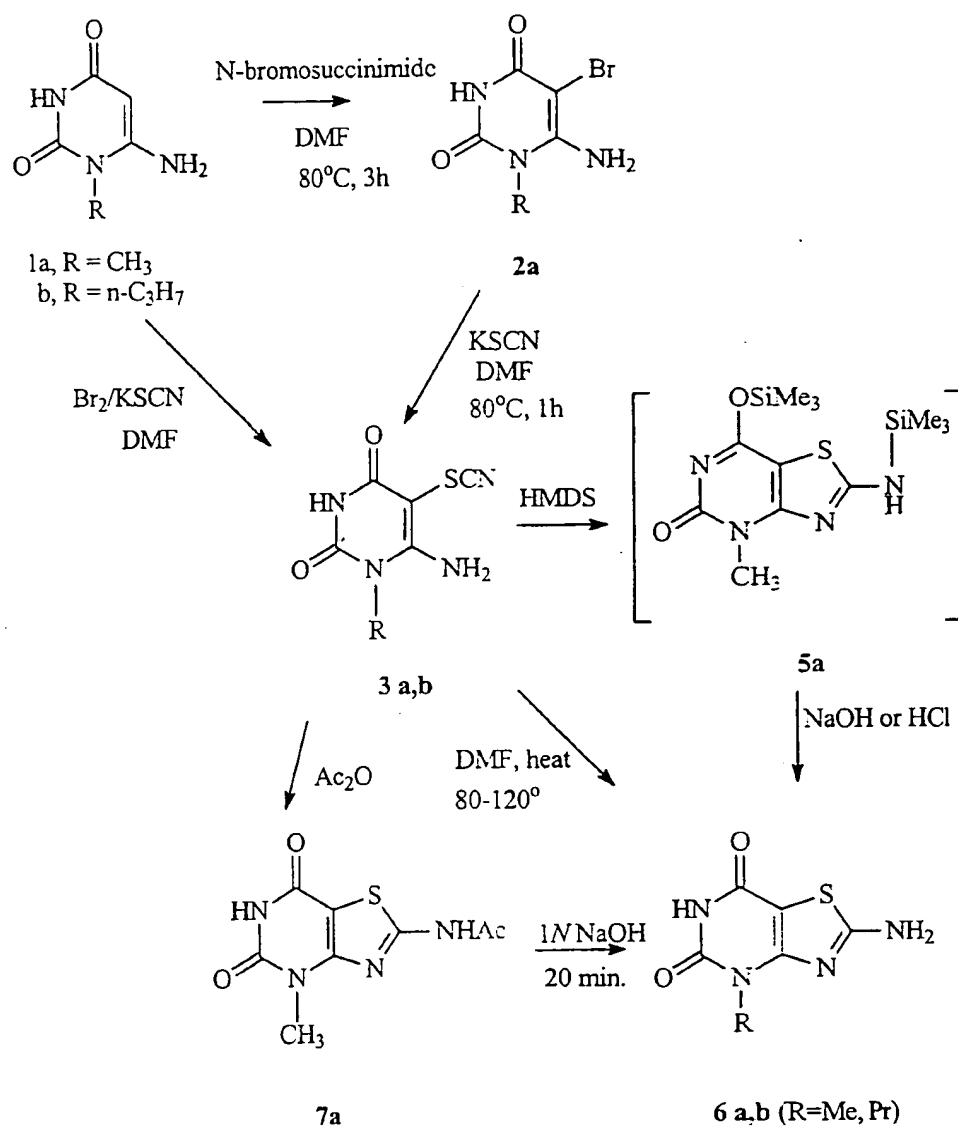


alcohol	ester	TNF inhib. (IC ₅₀)
EtOH	ethyl 8a	676 nM
	pyridinylpropyl 11-183	1.3 μM
	isopropyl 11-189	—
	ter-butyl 11-190	—
	hydroxypropyl 11-191	—

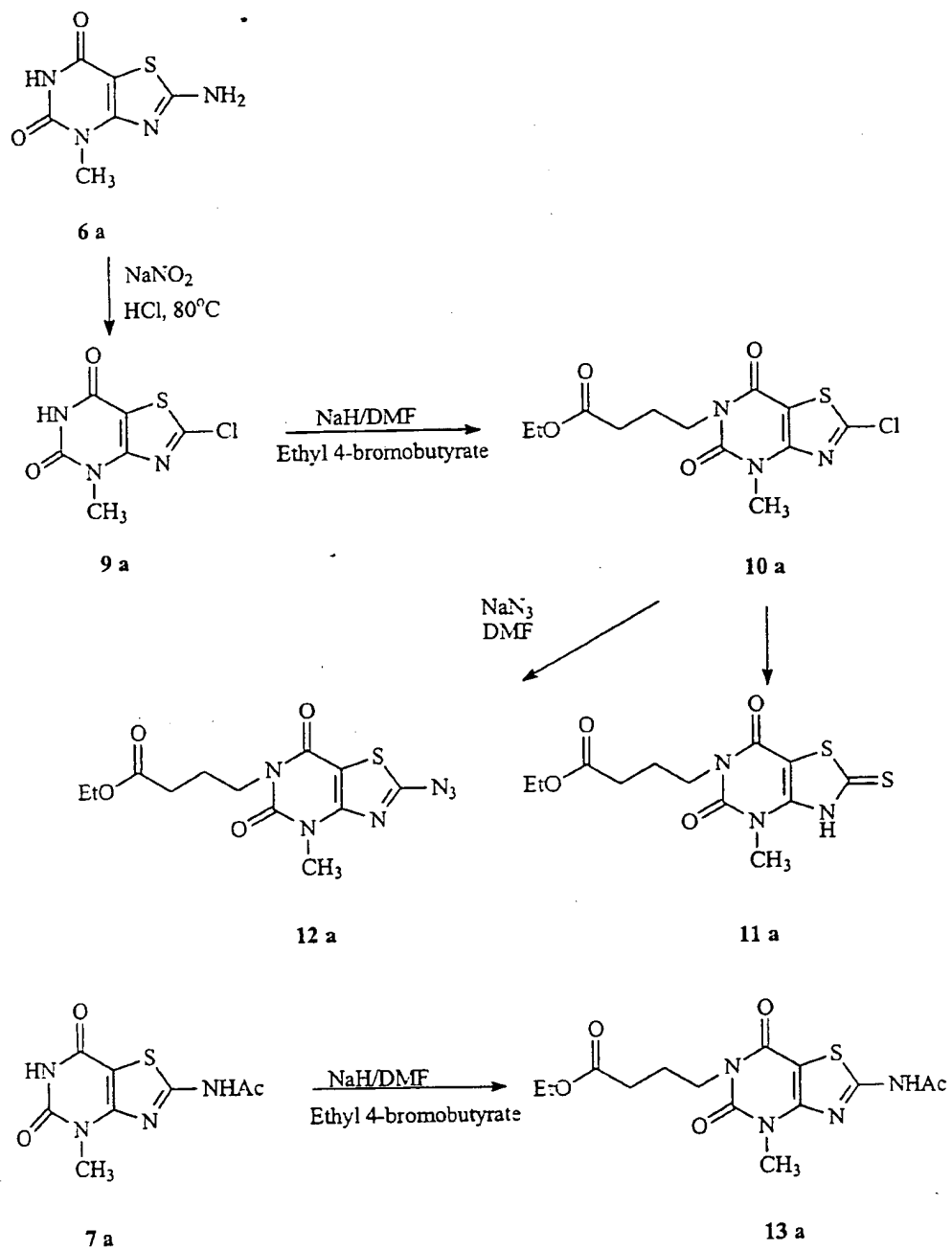
Scheme 1. L-Valine prodrug



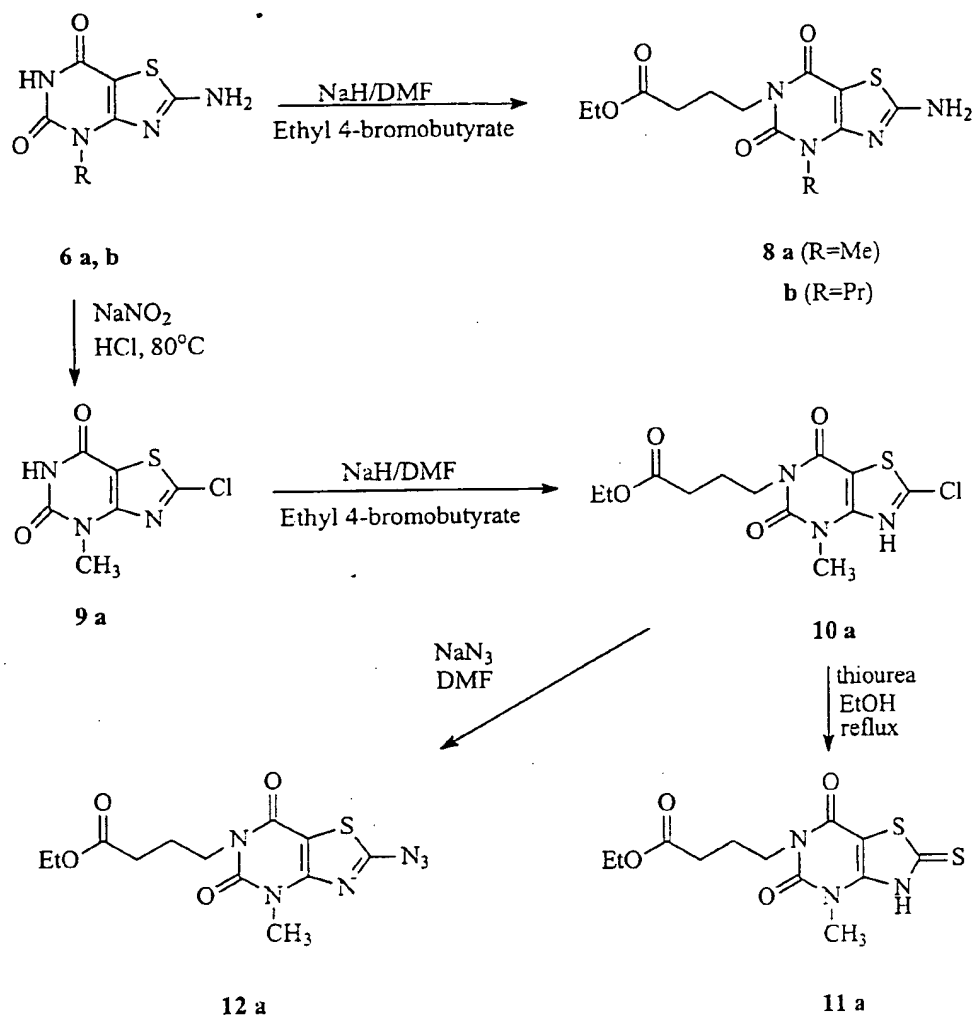
Scheme 2.



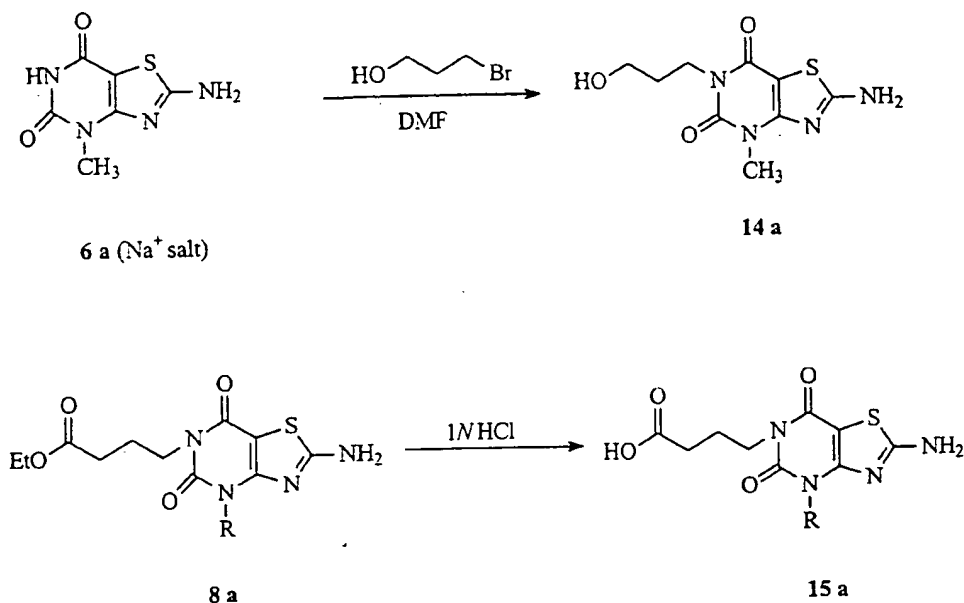
Scheme 3.



Scheme 4.



Scheme 5.



- Examples of pharmaceutically acceptable salts of compounds of formula (I) are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, malate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

- Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example, calcium) salts of carboxylic acids can also be made.

- The compounds of formula (I) can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant.

Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

- 5 The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparations of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable
- 10 under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the
- 15 formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for
- 20 example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

 Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the

25 other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

- 30 For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally
5 with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid composition can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

10 Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to
15 deliver the compounds of formula (I) to the skin are disclosed in Jacquet et al. (U.S. Patent No. 4,608,392), Geria (U.S. Patent No. 4,992,478), Smith et al., (U.S. Patent No. 4,559,157) and Wortzman (U.S. Patent No. 4,820,508).

Dosages of the compounds of the invention will vary depending on the age, weight and presenting condition of the host to be treated, as well as the
20 potency of the particular compound administered. Such variables will be readily be accounted for by those of ordinary skill in the clinical art. In particular, dosages will be adjusted upward or downward for each recipient based on the severity of the condition to be treated and accessibility of the target cells to the pharmaceutical formulations of the invention. Where possible, it will be
25 preferable to administer the pharmaceutical formulations of the invention locally at the site of the target cells; e.g., onto inflamed skin or by infusion to another organ of the host. Thus, dosages will also vary depending on the route of administration and the extent to which the formulations of the invention are expected to reach target cells before dilution or clearance of the formulation.

30 Generally, based on experience with other inhibitors of intracellular responses to external stimuli (such as pentoxifylline) and the data provided herein, good results can be expected to be achieved in an adult host of about 60 kg body weight in a dosage range of about 250 to about 4,000 mg/day,

preferably between about 1,000 and about 3,500 mg/day (i.e., a "therapeutically effective dosage"). These dosages may be combined with other conventional pharmaceutical therapies for inflammation and fibrosis; e.g., administration of non-steroidal anti-inflammatory medications.

5 The compounds of the invention vary in potency. Those of ordinary skill in the art will recognize that lesser or greater dosages of the compounds of the invention may be required depending on the potency of the particular compound being administered. Useful dosages of the compounds of formula (I) can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal
10 models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Those of ordinary skill in the art will be familiar with means to develop analogues to the compounds specifically described herein which, although not
15 structurally identical thereto, possess the same biological activity. Such compounds are within the scope of the invention and may be identified according to the protocols described below and in the examples.

Through exposure of cells to the compounds of the invention under controlled conditions, the responsiveness of cells to inflammatory agents and
20 intracellular mechanisms therefor can be investigated. This information will not only better elucidate the intracellular pathways responsible for cellular responses to particular stimuli, but will also aid in the identification of anti-inflammatory and anti-fibrosis therapeutic compounds.

To identify and select therapeutic compounds for use in treating
25 conditions such as inflammation and fibrosis, cells (or intracellular components such as microsomes) which have not been exposed to an inflammatory or fibroblast proliferation inducing agent (e.g., LPS, $\text{TNF}\alpha$, IL-1, PDGF) are exposed to such an agent and the candidate therapeutic compound. Specifically, a control group of cells is incubated with a known amount of the inflammatory
30 or fibroblast proliferation inducing agent. Treatment groups of cells are exposed to the same amount of inflammatory or fibroblast proliferation inducing agent as well as aliquots of the candidate therapeutic compound. Inflammatory responses or fibroblast proliferation in each group are detected by conventional means

known to those of skill in the art (such as the assay steps described in the examples) and compared.

To identify and select therapeutic compounds for use in treating conditions of cell senescence or apoptosis, cells (or intracellular components such as microsomes) which have not been exposed to a senescence or apoptosis inducing agent (e.g., cytokines such as $\text{TNF}\alpha$ and exogenous stimuli such as heat, radiation and chemical agents), are exposed to such an agent and to the candidate therapeutic compound. Inhibition of senescence or apoptosis is measured as a function of cell growth. Those of ordinary skill in the art will be familiar with techniques for obtaining such measurements, examples of which are provided below.

"Therapeutically effective compounds" will be those which, when administered according to the invention and sound medical practices, provide cells with protection against inflammation-associated conditions compared to control values for cellular reactions to a preselected inducing agent.

The invention having been fully described, examples illustrating its practice are set forth below. These examples should not, however, be considered to limit the scope of the invention, which is defined by the appended claims.

In the examples, the abbreviation "min." refers to minutes, "hrs" and "h" refer to hours, and measurement units (such as "ml") are referred to by standard abbreviations. "mp" refers to melting point.

Example 1

6-Amino-5-bromo-1-methyluracil (2a)

A mixture of 6-amino-1-methyluracil (14.0 g, 100 mmol), N-bromosuccinimide (21.0 g, 118 mmol), and dry DMF (250 mL) was heated at 80°C for 3 h. The reaction mixture was evaporated *in vacuo* and the residue was slurried with ice-cold 50% aqueous ethanol (150 mL) and filtered. The resulting off-white solid was washed with ethanol, then ether and dried to yield 18.0 g 2a (83%). mp 274°C dec; UV pH 1 λ_{max} 276 nm; NMR δ (DMSO- d_6) 3.26 (s, 3H, CH_3), 7.02 (s, 2H, NH_2), 10.89 (s, 1H, NH).

Example 2

2-Amino-4-methylthiazolo[4,5-d]pyrimidine-5,7-dione Sodium salt (6a)

A mixture of compound 11-160 (2a) (14.0 g, 64 mmol), potassium thiocyanate (14.0 g, 144 mmol) and DMF (250 mL) was heated at 80°C for 2 h and filtered hot to remove inorganics. The filtrate was evaporated to dryness *in vacuo* and hexamethyldisilazane (200 mL) was added and the mixture heated at 130°C for 30 min. The salmon-colored solid did not dissolve but ammonia was given off indicating some silylation occurred. The HMDS was decanted from the solid and 1N NaOH (150 mL) was added. The mixture was heated to near boiling for a few minutes whereupon the solid nearly dissolved and then the mixture became very thick again. The mixture was cooled on ice, triturated with ice-cold 50% aqueous ethanol and filtered. The solid was washed with cold ethanol, then ether and dried over P₂O₅ to yield 13.7 g. The crude product may be recrystallized from 1N NaOH to provide off-white microneedles of the sodium salt of 6a. mp > 320°C; UV pH 1 λ_{max} 223 nm (ϵ 13,400), 309 (8,100); pH 7 λ_{max} 223 nm (ϵ 17,100), 309 (10,500) pH 11 λ_{max} 218 nm (ϵ 17,500), 304 (8,800); NMR δ (DMSO-d₆) 3.33 (s, 3H, CH₃), 8.50 (s, 2H, NH₂), 11.05 (br s, residual NH).

Example 3

Ethyl 4-[2-Amino-4-methyl-5,7-dioxothiazolo[4,5-d]pyrimidin-6-yl]-butanoate (8a)

To a mixture of compound 11-173 (6a) (10.0 g, 45 mmol) and potassium carbonate (3.0 g) in dry DMF (200 mL) at 75°C was added ethyl 4-bromobutyrate (6.7 mL, 50 mmol) in one lot by syringe. The mixture was stirred at 75°C for 2 h, evaporated to dryness and the residue was partitioned between water (100 mL) and ethyl acetate (150 mL). The water layer was extracted with EtOAc (2 \times 75 mL) and the combined organic layer was dried over magnesium sulfate, filtered and evaporated onto silica gel (40 mL of 70-230 mesh silica gel 60). Flash column chromatography (5 \times 20 cm, 200-400 mesh) using 5% MeOH/CH₂Cl₂ gave 7.0 g (50%) of 8a as a yellow solid. mp 170-171°C; UV pH 1, 7, 11 λ_{max} 224 nm (ϵ 26,300), 309 (16,400); NMR δ (DMSO-d₆) 1.1 (t, 3H, terminal methyl of ethyl ester), 1.8 (m, 2H, C-3 methylene of butanoate), 2.3

(t, 2H, C-2 methylene), 3.4 (s, 3H, N-4 methyl), 3.8 (t, 2H, C-4 methylene), 4.0 (q, 2H, methylene of ethyl ester), 8.55 (s, 2H, amino).

Example 4

5 Inhibition of TNF α Production by the Compounds of the Invention

Peripheral blood mononuclear cells were isolated from normal human blood on Hypaque-Ficoll density gradients. 100 μ l aliquots of monocytes were placed onto 96 well microtiter plates at a density of 5×10^6 cells/well in RPMI-1640 medium containing 10% autologous plasma. After incubation for 24 hrs.,
10 various concentrations of the test compound in DMSO were added to the plated cells in a volume of 100 μ l and incubated for 1 hr. After incubation, 10 μ g/ml of LPS was added to each well.

Eighteen hours after exposure of the plated cells to LPS, 100 μ l of medium was collected from each well and assayed (by ELISA, R&D Systems)
15 for release of IL-1 and TNF α , using recombinant human TNF as a standard (n = 5). The sensitivity of the assay ranged from 10-100 pg/ml.

Figure 1 depicts the effect of compounds **8b**, **8a**, rolipram and SB-210313 on TNF α production. Rolipram is an inhibitor of phosphodiesterase-4, and has been reported to be a potent inhibitor of human TNF α production. SB-
20 210313 is an inhibitor of the p38 mitogen activated protein kinase, which was developed at Smith Kline Beecham, and has been reported to be a potent inhibitor of TNF α synthesis. **8b** (IC₅₀ = 421 nM) and **8a** (IC₅₀ = 676 nM) are more potent than rolipram (IC₅₀ = 2500 nM) or SB-210313 (IC₅₀ = 1146 nM).

Figure 2 summarizes the effects of **8b** and **8a** on the production of IL-1 β
25 by human monocytes stimulated with LPS, under the same conditions used for the TNF α study. Both compounds **8b** and **8a** also inhibit IL-1 production with a 50% inhibitory dose of about 1-3 μ M.

Example 5

30 Effect of **8a** and **8b** on Jurkat Cell Growth

In this experiment, cells of the continuous human lymphoblastoid Jurkat cell line were suspended at 1×10^5 /ml in complete medium containing various amounts of **8a** and **8b** dissolved in DMSO. Seventy-two hours later the cell

density was assessed using the MTT assay, which measures the reduction of a tetrazolium dye. The cell densities were compared to control cultures lacking any additional drugs. Note that neither **8b** nor **8a** had significant growth inhibitory activity at a concentration below 50 μ M.

5

Example 6

Inhibition of Phosphodiesterase IV Activity by Compounds of the Invention

Phosphodiesterase type 4 is a target for inhibitors of $\text{TNF}\alpha$ synthesis such as rolipram. Therefore, the effects of **8b** and **8a** on the PDE4 enzyme
10 purified from the U937 human monocyte cell line were evaluated. Extractions of this cell line were separated on a Sephadex column and the rolipram inhibitable fractions were isolated. PDE4 was assayed by a commercial radioassay that measures the conversion of ^3H -cyclic AMP to AMP and subsequently to adenosine, as assessed by ion exchange chromatography. The reaction was
15 started with the addition of PDE and incubated at 37°C for 10 minutes, then terminated by boiling for 2 minutes. After completion of the reaction, 5'-nucleotidase (Sigma) was added to convert all AMP to adenosine. Then a Dowex[®]-I slurry was added to absorb the negatively charged ^3H -cAMP. 500 μ l of 0.1 M HEPES/0.1 M NaCl (pH 8.5) was added to each tube, then the reaction
20 mixture was applied to the column. Unreacted cAMP was washed off with Hepes/NaCl and the reaction mixture eluted with acetic acid. Recovery was determined with the ^{14}C -AMP.

As shown in Figure 4, the test compound rolipram inhibited PDE4 with an IC_{50} of 196 nM. In contrast, the IC_{50} values for **8a** were 43 μ M and 2.1 μ M,
25 respectively. These values contrast strongly with the potencies of the compounds as inhibitors of $\text{TNF}\alpha$ synthesis. This experiment rules out the possibility that **8a** and **8b** act principally by inhibition of PDE4.

Example 7

Acute Toxicity Testing

30

ICR mice (ca. 20 g) were injected IP for 5 days with 50 mg/kg, and 100 mg/kg of each of **8a** and **8b** dispersed in aqueous hydroxypropyl β -

cyclodextrin (50% w/v). Five daily IP injections at 100 mg/kg produced no weight change or detectable lethargy in the mice over 30 days of observation.

Example 8

5 In Vivo Effects of Orally Administered 8a

ICR mice were dosed orally at 25, 50 and 100 mg/kg of **8a** in cyclodextrin, prepared as in Example 7. After 1 hr., each mouse was injected with *E. coli* LPS (1 µg/mouse). Two hours later, 250 µl samples of blood were obtained by retro-orbital bleeding without anesthetization. The blood was
10 heparinized, centrifuged for 10 min. at 10 K rpm (4°C) and TNFα determined by ELISA. As shown in Fig. 5, even 25 mg/kg of **8a** had a significant inhibitory effect on TNFα plasma concentration, which was greater at 50 mg/kg. The two bars at the top of the figure show the baseline levels of TNFα in the mouse plasma, which were undetectable, and the effects of **8a** administered alone,
15 which were negligible.

Example 9

Time Course Study of TNFα Inhibition

The purpose of these experiments was to determine how long after
20 administration of compound **8a** by gavage could its inhibitory effects on LPS-induced TNFα production be detected. Accordingly, all the ICR in this instance were given **8a** at a dosage of 100 mg/kg by gavage. Then at 1, 4, 10, and 24 hours later, each animal received 1 µg/ml IP LPS, and two hours later (i.e., at 3, 6, 12, and 26 hours), blood was removed for TNFα ELISA. As shown in
25 Figure 6, even after 24 hours, **8a** at this high dosage completely inhibited the accumulation of TNFα in the plasma of LPS-injected mice. These experiments demonstrate that **8a** is orally active, and has a relatively long biological effect *in vivo*.

30

Example 10

Inhibition of Adjuvant Arthritis

Since TNFα antagonists have shown considerable value in the treatment of rheumatoid arthritis, compound **8a** was evaluated in an animal model that is

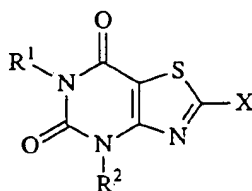
TNF α dependent. Adjuvant arthritis is an acute inflammatory disease induced in certain rat strains by the administration of heat-killed mycobacteria dispersed in incomplete Freund's adjuvant. The disease is manifest by severe joint swelling, mainly of the ankles and feet.

5 Two groups of seven Lewis rats each were immunized intradermally with 5 mg of heat-killed mycobacterium tuberculosis emulsified in incomplete Freund's adjuvant. One day later, one group of animals (N = 7) received 100 mg/kg of 8a by gavage. Another group of animals received no treatment. The oral dosing was continued every day up to day 30. The clinical scores of the
10 animals were determined every other day at day 14 by an observer who did not know which group had been treated. The results are shown in Figure 7. The mean arthritis score can vary from 0 to 4 for each limb, yielding a maximum score of 16. Note that the untreated animals (group 1) achieved a mean arthritis score of 10 on day 18. In contrast, the treated animals reach a mean arthritis
15 score of 5, for 50% inhibition. These results are statistically significant at the p < 0.05 level.

 All publications, patents and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred
20 embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of formula (I):



(I)

- 5 wherein R¹ is -Z-A wherein Z is (a) C₁-C₇ alkyl, optionally comprising 1-2 double bonds, 1-2 nonperoxide O or 1-2 NR wherein R is individually H, phenyl, benzyl, C₂-C₄ alkanoyl or C₁-C₆ alkyl; (b) C₃-C₆ cycloalkyl; (c) C₃-C₆ cycloalkyl C₁-C₃ alkyl; (d) C₆-C₁₀ aryl; or (e) C₆-C₁₀ aryl C₁-C₃ alkyl;

A is N(R)₂, C₂-C₄ acyloxy, SO₃H, PO₄H₂, N(NO)(OH), SO₂NH₂,

- 10 PO(OH)NH₂, OH, SO₂R³ tetrazolyl, or COOR³ wherein R³ is H, phenyl, benzyl or C₁-C₆ alkyl optionally substituted with 1-2 OR, C₆-C₁₀ heteroaryl, C₆-C₁₀ aryl, C₂-C₄ alkenyl, phenyl, tetrazolyl or an ester of an amino acid;

R² is a C₁-C₆ alkyl, C₂-C₄ alkenyl, C₆-C₁₀ aryl C₁-C₂ alkyl or C₆-C₁₀ heteroaryl C₁-C₂ alkyl;

- 15 X is H, halo, OR, SR, N₃ or N(R)₂; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein Z is (C₂-C₆)alkyl or phenyl.

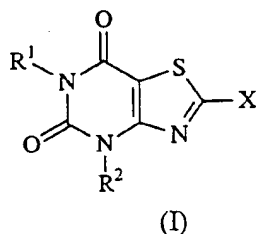
- 20 3. The compound of claim 1 or 2 wherein A is CO₂R³.

4. The compound of claim 3 wherein R³ is H or (C₁-C₆)alkyl, optionally substituted with OH, C₆-C₁₀ heteroaryl or an ester of an amino acid.

- 25 5. The compound of claim 4 wherein the ester of the amino acid is an L-valine residue or L-glycine residue.

6. The compound of claim 4 wherein R^3 is (C_1-C_6) alkyl substituted with 4-pyridyl.
7. The compound of claim 1 or 2 wherein -Z-A is ethoxycarbonylpropyl.
- 5 8. The compound of claim 1 or 2 wherein X is NH_2 .
9. The compound of claim 1 or 2 wherein R^2 is CH_3 , CH_2CH_3 or $CH_2CH_2CH_3$.
- 10 10. A pharmaceutical composition comprising the compound of claim 1 in combination with a pharmaceutically acceptable carrier.
11. The use of the compound of claim 1 as a medicament.
- 15 12. The use of the compound of claim 1 as a medicament to treat a pathological condition associated with the overproduction of proinflammatory cytokines.
- 20 13. The use of claim 12 wherein said condition comprises a pathological inflammatory response.
14. The use of claim 13 wherein said inflammatory response is due to arthritis.
- 25 15. The use of claim 13 wherein said inflammatory response is due to an autoimmune disease.
16. The use of claim 15 wherein said autoimmune disease is rheumatoid
- 30 arthritis, multiple sclerosis, asthma, psoriasis or inflammatory bowel disease

17. The use of claim 12 wherein said condition comprises cardiomyopathy or congestive heart failure.
18. The use of claim 12 wherein said condition comprises insulin-resistant
5 diabetes.
19. A method of inhibiting release of an inflammatory cytokine by a mammalian cell, the method comprising contacting the cell with an amount of a compound of claim 1 effective to inhibit the release of the inflammatory
10 cytokine.
20. The method of claim 19 wherein the cytokine is TNF- α .
21. The method of claim 19 wherein the cytokine is IL-1.
- 15 22. A pharmaceutical composition comprising a compound of formula (I):



- wherein R¹ is -Z-A wherein Z is (a) C₁-C₇ alkyl, optionally comprising 1-2 double bonds, 1-2 nonperoxide O or 1-2 NR wherein R is individually H, phenyl, benzyl, C₂-C₄ alkanoyl or C₁-C₆ alkyl; (b) C₃-C₆ cycloalkyl; (c) C₃-C₆ cycloalkyl
20 C₁-C₃ alkyl; (d) C₆-C₁₀ aryl; or (e) C₆-C₁₀ aryl C₁-C₃ alkyl;
- A is N(R)₂, C₂-C₄ acyloxy, SO₃H, PO₄H₂, N(NO)(OH), SO₂NH₂, PO(OH)NH₂, OH, SO₂R³ tetrazolyl, or COOR³ wherein R³ is H, phenyl, benzyl or C₁-C₆ alkyl optionally substituted with 1-2 OR, C₆-C₁₀ heteroaryl, C₆-C₁₀ aryl, C₂-C₄ alkenyl, phenyl, tetrazolyl or an ester of an amino acid;
- 25 R² is a C₁-C₆ alkyl, C₂-C₄ alkenyl, C₆-C₁₀ aryl C₁-C₂ alkyl or C₆-C₁₀ heteroaryl C₁-C₂ alkyl;

X is H, halo, OR, SR, N₃ or N(R)₂; or a pharmaceutically acceptable salt thereof;

in combination with a carrier; wherein the composition is suitable for oral administration.

5

23. The composition of claim 22 wherein Z is (C₂-C₆)alkyl or phenyl.

24. The composition of claim 22 or 23 wherein A is CO₂R³.

10 25. The composition of claim 24 wherein R³ is H or (C₁-C₆)alkyl, optionally substituted with OH, C₆-C₁₀ heteroaryl or an ester of an amino acid.

26. The compound of claim 25 wherein the ester of the amino acid is an L-valine residue or L-glycine residue.

15

27. The compound of claim 25 wherein R³ is (C₁-C₆)alkyl substituted with 4-pyridyl.

28. The compound of claim 22 or 23 wherein -Z-A is ethoxycarbonylpropyl.

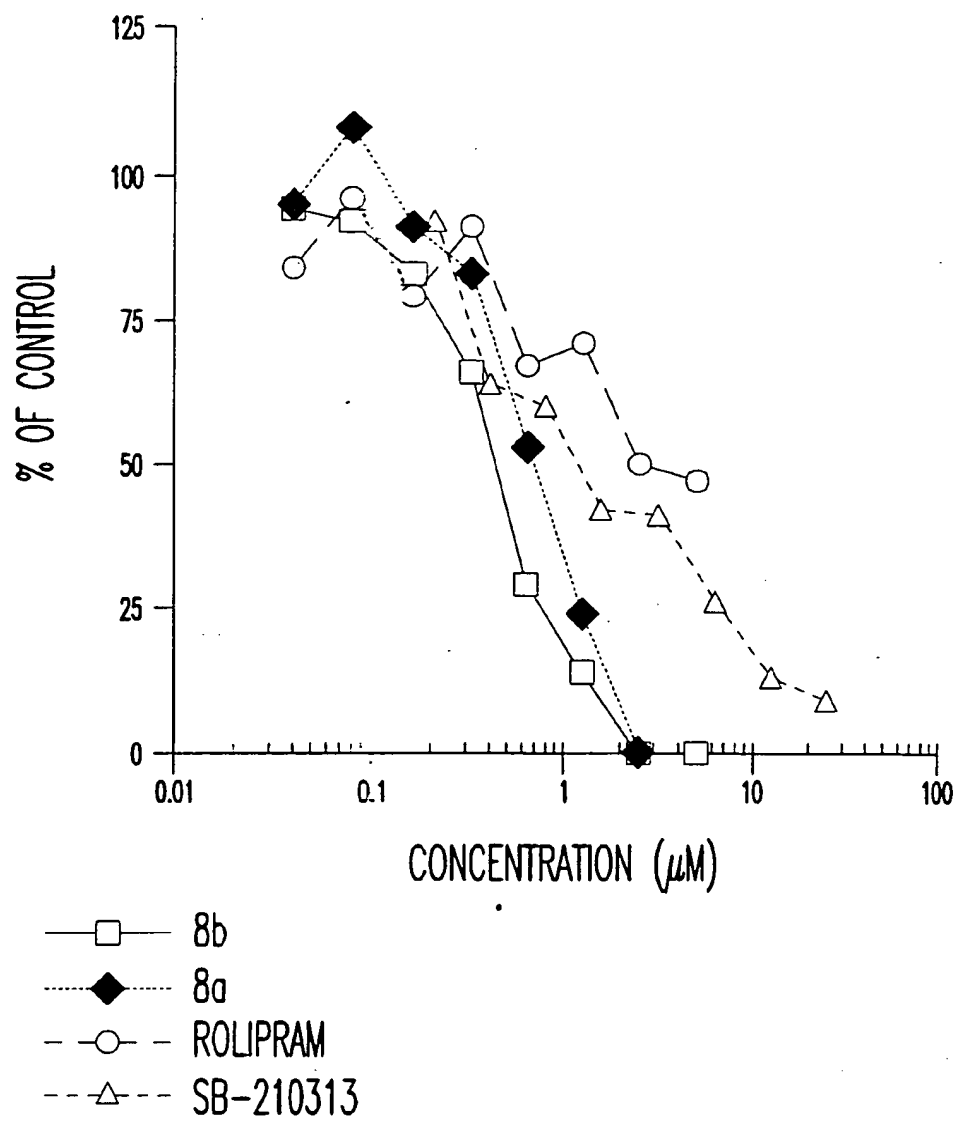
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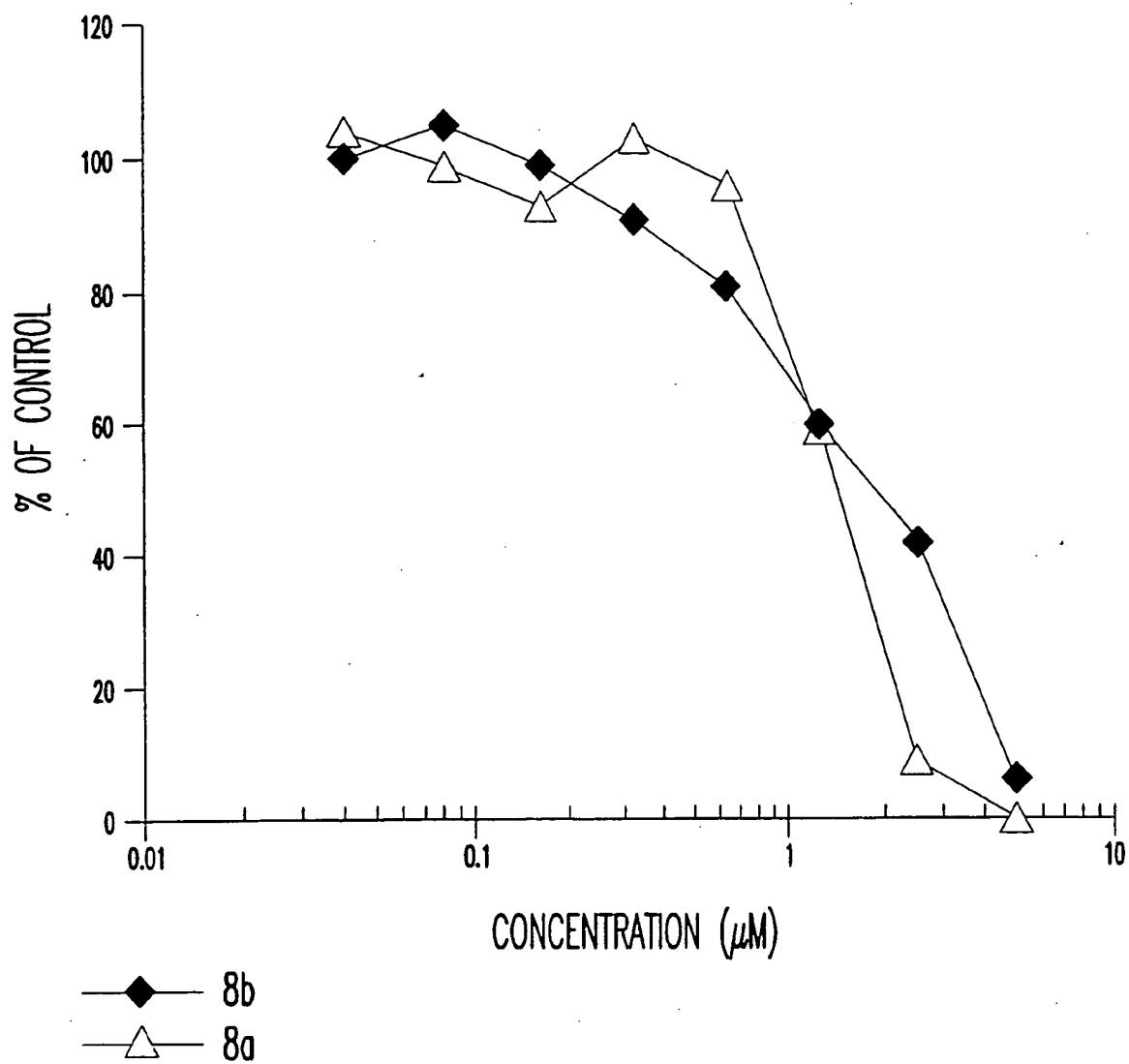
29. The compound of claim 22 or 23 wherein X is NH₂.

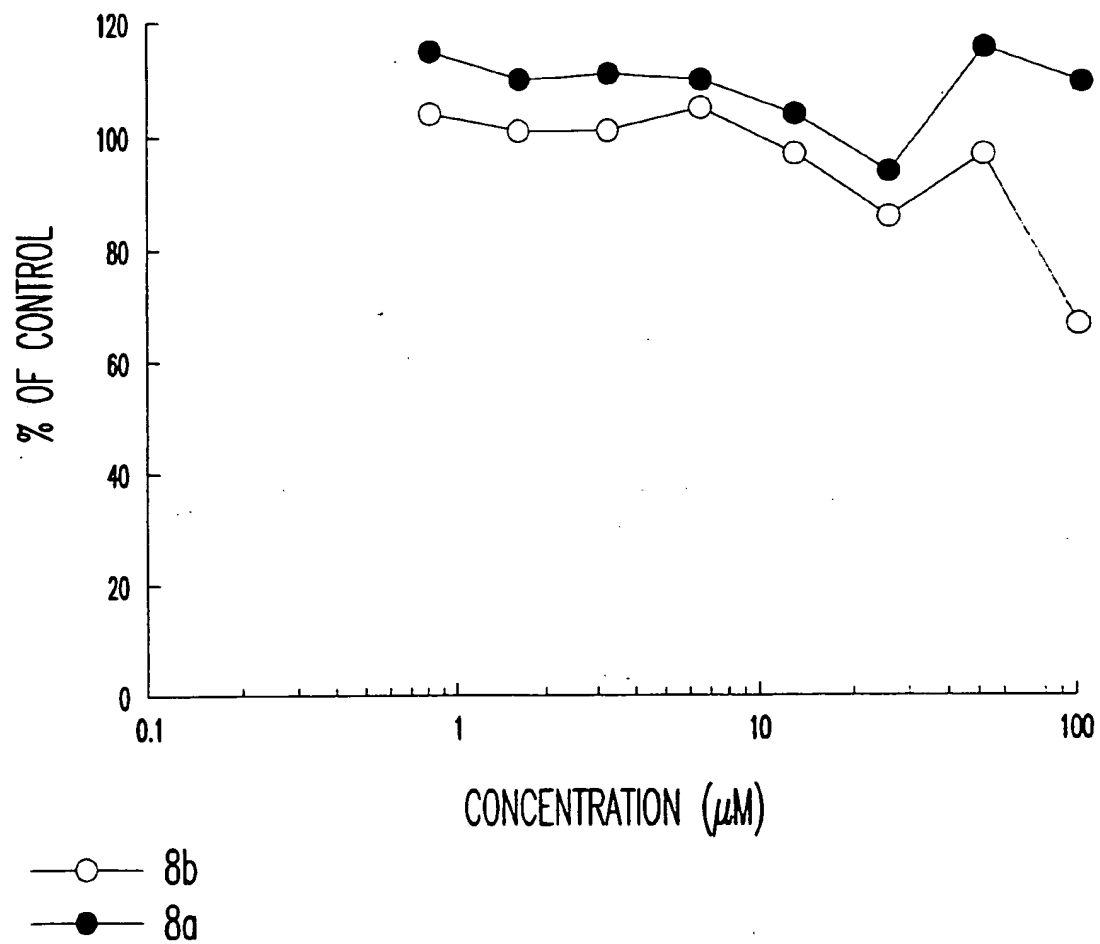
30. The composition of claim 22 or 23 wherein R² is CH₃, CH₂CH₃, or CH₂CH₂CH₃.

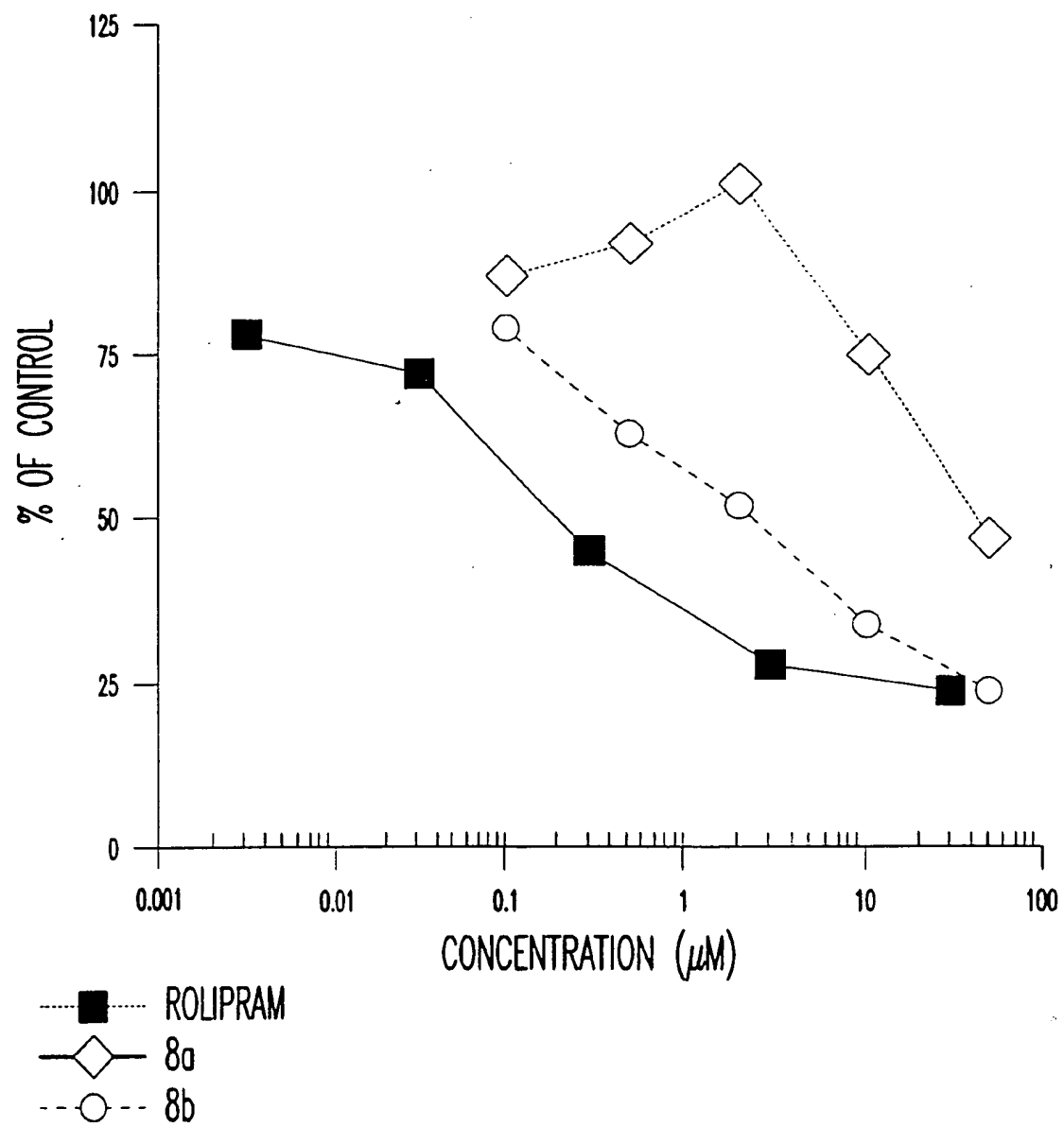
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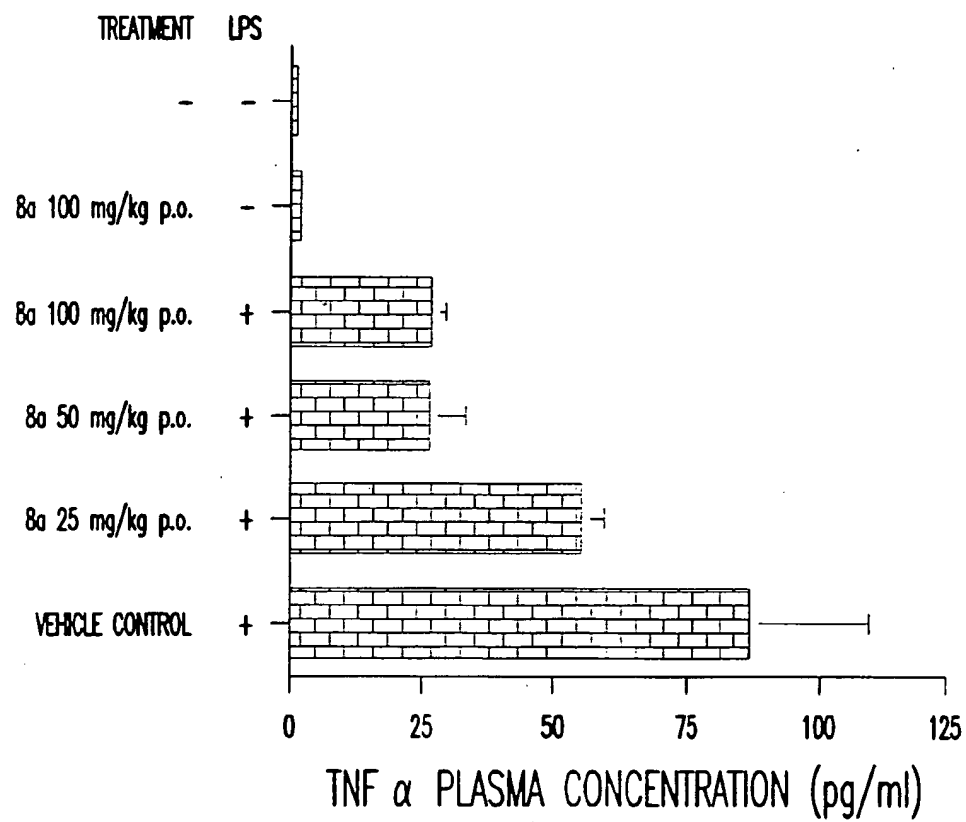
31. The composition of claim 22 or 23 wherein the composition is an aqueous solution, an aqueous dispersion, a powder, a gelatin capsule, or compressed into a tablet.

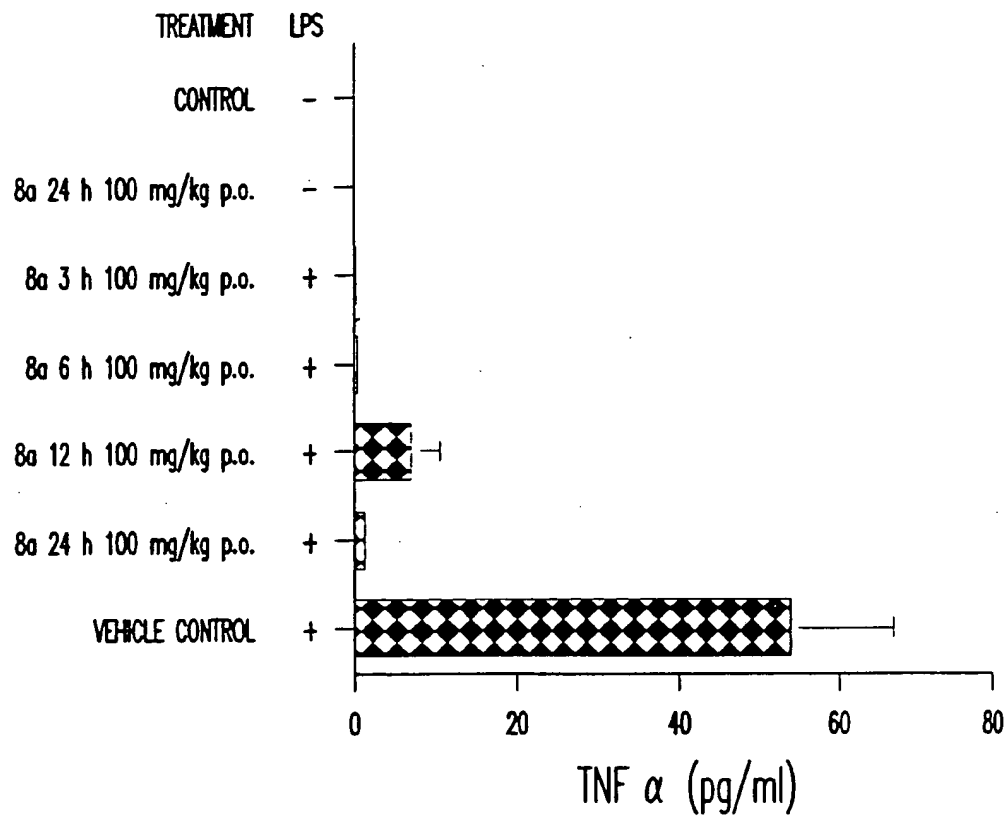
*Fig. 1*

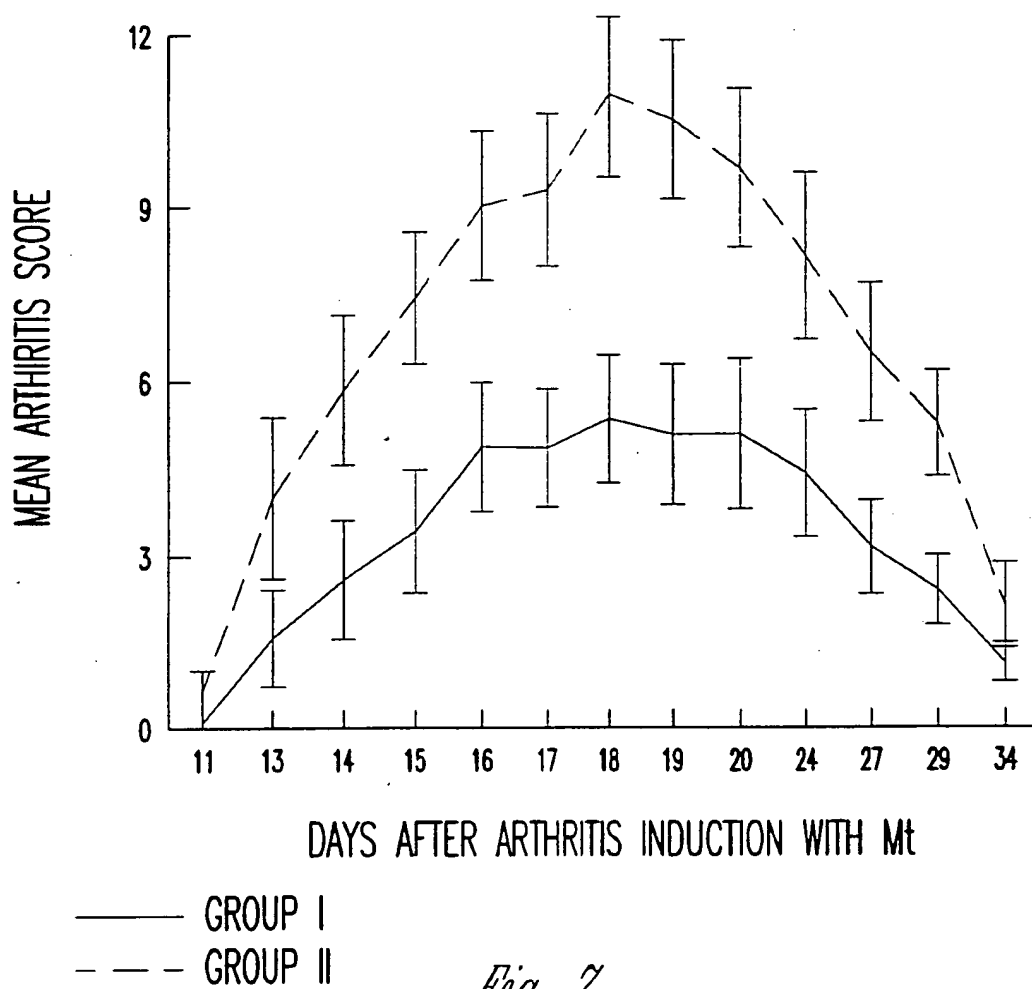
*Fig. 2*

*Fig. 3*

*Fig. 4*

*Fig. 5*

*Fig. 6*

*Fig. 7*

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/13410

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D513/04 A61K31/519 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 22464 A (DARWIN DISCOVERY LIMITED) 28 May 1998 (1998-05-28) the whole document ---	1-31
A	WO 93 16699 A (SMITHKLINE BEECHAM CORPORATION) 2 September 1993 (1993-09-02) the whole document ---	1-31
A	US 5 877 180 A (JOEL M. LINDEN ET AL.) 2 March 1999 (1999-03-02) cited in the application the whole document ---	1-31
A	US 5 843 943 A (DENNIS A. CARSON ET AL.) 1 December 1998 (1998-12-01) cited in the application the whole document ---	1-31
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

25 September 2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/13410

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim no.
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